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Prognostic value of combined assay of total estrogen and pregnanediol in 24 hour urine. Experience with 500 pregnancies in an endocrine surveillance program during the second trimester*

R. Wolfrum, Ch. Bordasch, J. Holweg, G. Schulz, U. Schulz, W. Oelkers

Section of Perinatal Medicine, Allgemeines Krankenhaus Heidberg, Hamburg

Hormonal analyses have become indispensable for managing high-risk pregnancies. They allow an early diagnosis of chronic disturbances in the nutritive function of the placenta and of fetal growth retardation. However, except for a few clinics [2, 9] hormonal assays are frequently used only when the placental dysfunction is already clinically manifest (premature labor, discrepancy between uterine size and estimated gestational age, etc.) or if there are serious risk factors from the history. Not infrequently "placental insufficiency" is not accompanied by any clinical symptoms [10, 18] and thus escapes diagnosis, or at least early diagnosis. Early diagnosis, however, is the decisive prerequisite for successful therapy which must have its goal a mature healthy newborn with a normal birth weight.

Biochemical parameters in contrast to clinical and biophysical obstetric indicators are currently the only ones which give any direct information about the function of the placenta. Measurements of placental perfusion with radioisotopes cannot be used in clinical routine as yet. Therefore, hormonal assays should indicate disturbances in placental function earlier than the other variables. Thus, the medically correct procedure would consist of hormonal assays for all pregnant women as a preventive measure, thus facilitating either exclusion or early diagnosis of a placental risk. A **suitable endocrine surveillance program for pregnant patients prior to the 30th week leading to a marked decrease of the number of small-for-dates infants has not been described to date.**

We have recently published an endocrine model [18] in which we postulate that generally there is a primary impairment of placental function and that fetal manifestations are secondary (except for primary fetal anomalies). An endocrine surveillance program for the early recognition of placental functional disturbances should therefore primarily utilize placental indicators. The estrogen excretion in the urine as well as the estriol concentration in the plasma is an early fetal but not an early placental indicator [9, 18]. Therefore, we interpret pathological excretions of estrogen as representing already present fetal damage and consequently we attempt to avoid this advanced stage of disturbed fetoplacental function. A suitable early placental indicator in our experience is the urinary excretion of pregnanediol [18] and somewhat less the concentration of human placental lactogen (HPL) in the serum [WOLFRUM, to be published]. The present study attempts to give further proof of the usefulness of the described model. Thus the determination of total estrogen was included in the program. In addition, the study was to answer three questions:

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1. What is the earliest time at which "placental insufficiency" can be diagnosed by means of pregnanediol excretion?
2. Is it possible to predict the future function of the placenta and the further growth of the fetus from hormonal findings between the 20th and 30th week of gestation?
3. Is it possible to decrease significantly the number of premature and dysmature births by early diagnosis and appropriately timed preventive measures?

1 Material and Methods

Analytical methods described earlier [19, 20] and controls [18] were used. The preventive program admitted at no cost pregnant women who were at least in the 19th and not beyond the 23rd week of gestation. Delivery in our hospital was not a condition for acceptance into the program. The contact with patients was maintained through an informational brochure via the practicing obstetricians. Each patient had a determination of the biparietal skull diameter by ultrasound in order to verify the estimated date of confinement. If the calculated gestational age from the last menstrual period and the ultrasonographic findings deviated from each other by more than two weeks, the patient was measured again with ultrasound four weeks later. At the first clinic visit each patient was extensively informed about the purpose of the program and the technique of urine collections. After the ultrasonography, three combined estrogen and pregnanediol determinations were carried out at intervals of two weeks. Thus, the program extended from the 20th to the 27th week of gestation.

Pregnanediol excretion was considered pathological if at least two of the three values were below the potentially pathologic range (Fig. 1).

The estrogen excretion was considered pathological (Fig. 1), if:

1. either at least two of the three values were in the potentially pathological range or below and if the excretion did not increase, or
2. if all three values were below the potentially pathological range, or
3. if there was a successive decrease in the excretion within the normal range.

With an interpretation of either the pregnanediol excretion or the estrogen excretion alone as pathological the entire analysis was considered abnormal. If the hormonal findings were normal, the patient was not further examined unless there was a high-risk history. With pathological hormonal results the patients were monitored further but at shorter time intervals (1–3 hormonal assays per week including HPL determination and biweekly ultrasonography including thorax diameter).

Between the 30th and 33rd week the hormonal patterns were evaluated again. Patients with increased pathological hormonal findings and clinical risk factors (toxemia, etc.) were cared for in an intensive special program until delivery; they accounted for about 10% of the total group and will be reported on separately. "Borderline" findings without clinical symptomatology did not lead to intensive monitoring; these patients were given general preventive advice such as stopping to work,

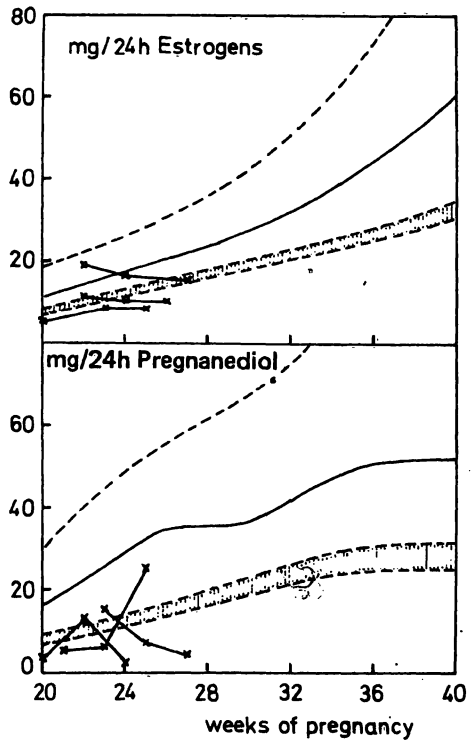

Fig. 1. Examples of pathological hormonal excretion as defined in the text. The curves represent estrogen and pregnanediol values from six separate pregnancies.

avoidance of stress, and proscription of smoking but there were occasional hormonal and ultrasound controls.

We define "placental risk" as follows:

1. History: one or more perinatal deaths (except for unequivocally non-placental causes of death) or one or more children with a birth weight of equal to or under 2700 grams or two or more abortions or severe toxemia.
2. Current pregnancy: placental weight less than 500 g* or macroscopically markedly infarcted placenta or pathological findings in the placental histology** or hypertension in early pregnancy*** or threatened abortion or elderly primipara (over 32 years) or elderly multipara (over 40 years) or young primipara (under 20 years). The presence of even one risk factor from history or current pregnancy was considered as indicative of "placental risk." Only one factor was applied to each patient. If several factors were present, the clinically more severe was used: current pregnancy over past pregnancies, dead fetus over hypotrophic fetus, hypotrophic fetus over toxemia, placental weight or abnormal histology over hypertension, etc.

The results of the hormonal assays were statistically related to birth weight and "placental risk." The surveillance program exists since early 1974; therefore, we compared premature and dysmature births in our clinic from 1973 to 1975 in order to determine any change in the outcome during that time.

Statistical calculations used the chi square test for normal distribution, the four fild chi square test, and the t-test.

To determine the gestational age and maturity of the infant in the surveillance group we utilized the ultrasound findings (biparietal skull diameter) from the 19th to 20th week, the maturation index of PETRUSSA [15] and also the menstrual history. In all other cases the menstrual history was used primarily as well as length [13] and head circumference [13] of the infant for determination of maturation. The boundary between appropriate-for-dates newborns and small-for-dates infants is generally taken to be the 10th percentile of LUBCHENCO [13]. For infants born at 40 weeks this is 2600 grams. Some newer findings from Europe [3, 12, 14] have shown that the limit in this social, economic, geographic and ethnical environment is higher [9]. In order to account for this fact and to make comparisons possible [9] we drew the limit at 2700 grams. This corresponds to the 15th percentile of Lubchenco. Locally applicable percentiles are not yet known. Newborns from the beginning of the 38th week were considered as mature [9]. Otherwise newborns with a weight of equal to or under 2700 grams were classified as described by KLINGMÜLLER-AHTING et al. [9] as hypotrophic mature, eutrophic premature, and hypotrophic premature. Correspondingly, the 15th percentile of Lubchenco was used. Twins were excluded from these statistics.

2 Results

2.1 Correlation between birth weight and hormonal assays

The birthweights of the infants with normal assays and of those with pathological results of hormonal assays were tested with the chi square test as to normal distribution. It was found that for the group with pathological hormonal assay, $\chi^2 = 5.443$. The significance threshold for $p = 0.05$ for 5 degrees of freedom is $\chi^2 = 11{,}070$. For the group with normal hormonal assay it was found that $\chi^2 = 5{,}004$. The level of significance for $p = 0.05$ for 8 degrees of freedom is $\chi^2 = 15.507$. Thus the distribution of frequency for the birthweights in both groups can be considered as normal and consequently the t-test may be used for a test of significant differences. The average birth weight of all children with normal hormonal findings was 3468 grams, for those with pathological results it was 3210 grams. The difference in the t-test is highly significant ($p < 0.001$). This expresses the fact that in the group with pathological hormonal findings children with relatively low birth weights

* Mean placental weight: 600 grams (N = 396 pregnant patients from the above described group; Range 260–960 g).

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*** Toxemia occuring during and other factors late pregnancy which are difficult to assess such as smoking, stress, etc. were not considered.

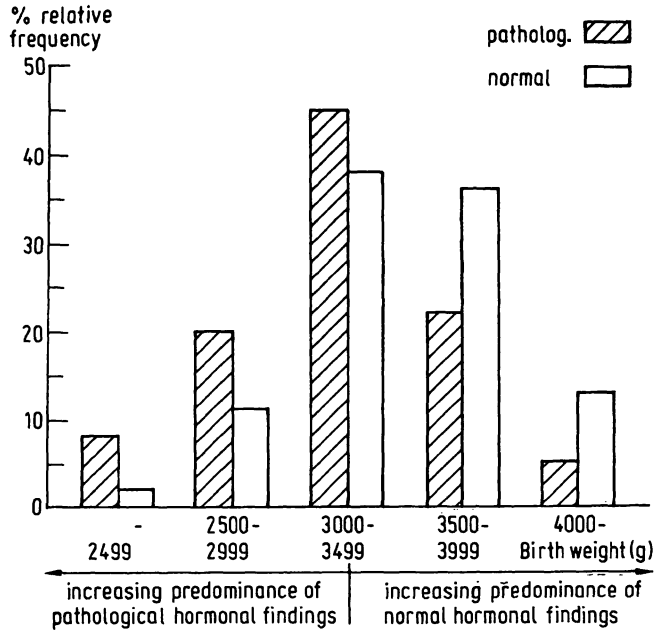

Fig. 2. Three combined estrogen and pregnanediol determinations in 500 pregnant patients between the 20th and 27th week. The 500 newborns are classified in five weight categories (five dual columns). In each weight category infants from pregnancies with pathological hormonal assays (hatched columns) are compared with those from pregnancies with normal hormonal findings (blank columns).

are over-represented. Obviously, a pathological hormonal assay does not in every case predict a low birth weight infant. Results are summarized in Tab. I and Fig. 2.

2.2 Correlation of "placental risk" with hormonal assay findings

Among the 500 pregnancies of the surveillance program there were 208 (41.6%) with "placental risk." The classification as to the separate factors is given in Tab. II.

About 25% of all pregnancies are risk pregnancies [16]. If the placental contribution is estimated as two-thirds then it is seen that our surveillance program did not deal with an unselected group since it comprises in comparison to a hypothetical normal cohort more than twice the proportion of placental risk cases. We found 381 cases of normal hormonal excretion, 105 cases of pathological pregnanediol excretion, 4 times pathological estrogen and pregnanediol excretion (Tab. I). The endocrine status was thus pathological in 119 cases (23.8% of all pregnancies).

Tab. I. Classification of pregnancies into risk groups according to the combined estrogen and pregnanediol excretion. Mean birth weight is correlated with hormonal findings. Cases with "placental risk" are correlated to hormonal findings. The frequency of hypotrophic newborns and eutrophic prematures is indicated.

E = total estrogen excretion; P_2 = pregnanediol excretion; n = normal; p = pathological.

Result of hormone assays	risk group	N	overall endocrine status	number with "placental risk"	four field chi square test: hormonal status vs "placental risk"	mean birth weight (g)	t-test: hormonal status vs mean birth weight	number of hypotrophic newborns ⩽ 2700 g	number of eutrophic prematures ⩽ 2700 g
E n P_2n	I	381	n	138 (36.2% of N)		3468		3 (0.7% of N)	14 (3.6% of N)
E n P_2p	II	105	p		$p < 0.001$ i.e. "placental risk" significantly more often with pathological hormonal status		$p < 0.001$ i.e. mean birth weight significantly lower with pathological hormonal status		
E p P_2n	III	4	p						
E p P_2p	IV	10	p	70 (58.8% of N)		3210		15 (12.6% of N)	3 (2.5% of N)

Tab. II. "Placental risk" according to individual placental risk factors

Placental risk factors	Past history: previous perinatal deaths	Past history: previous infants ⩽ 2700 g	Past history: two or more abortions	Past history: toxemia	Current pregnancy: pathological placental histology	Current pregnancy: placental weight ⩽ 500 g	Current pregnancy: grossly infarcted placenta	Current pregnancy: hypertension in early pregnancy	Current pregnancy: threatened Ab.	Current pregnancy: elderly primipara > 32y.	Current pregnancy: young primipara < 20y.	Current pregnancy: elderly multipara > 40y.
n	21	31	3	3	5	68	7	27	17	21	4	1
N = Σ n						208						
% of N	10.1	14.9	1.4	1.4	2.4	32.7	3.4	13.0	8.2	10.1	1.9	0.4

After the very highly significant correlation between pregnanediol excretion and nutritive placental function had been found, we tested with the four field χ^2 test whether the group with pathological hormonal findings contained significantly more "placental risk" (70 times = 58.8% of our cases with pathological hormonal findings) than the group with normal hormonal status (138 times = 36.2% of all cases with normal hormonal findings). The test is highly significant ($p < 0.001$).

In combination with the positive correlation between birth weight and hormonal findings, it is thus shown that the named "placental risk factors" are indeed placental risk factors with a potential impairment of the nutritive function. These results are summarized in Tab. I. According to our model most of the later hypotrophic newborns (10 of 15) | are still in risk group II (only pathological pregnanediol findings) at this stage of pregnancy.

In 48 cases there was no "placental risk", yet the hormonal findings were thought to be pathological (40.3% of all pathological hormonal findings). Of these pregnancies 45 ended with the birth of a mature, normal-weight infant, one with prematurity, and two with dysmaturity.

Cases with "placental risk" in the history and currently normal findings were analysed separately. There were 41 such pregnancies. It was seen that with normal hormonal findings in 39 cases (95.1%) a mature, normal-weight child was born (one eutrophic premature with 2500 grams/47 cm and a hypotrophic mature with 2650 grams/48 cm).

Cases with normal hormonal status resulting in a low weight infant were analysed separately. There were 17 such pregnancies (3.4%). In 14 cases (2.8%) the children were eutrophic prematures and in 3 cases (0.6%) hypotrophic mature infants (2460 g, 2650 g, 2700 g). The number of falsely normal hormonal assays resulting in hypotrophic newborns thus is less than 1% of all births (16.6% of all hypotrophic newborns). The distribution of hypotrophic newborns and eutrophic prematures in risk group I and II–IV is shown in Tab. I.

2.3 Comparison of premature and dystrophic infants

After the high predictive accuracy for diagnosis and prognosis in our surveillance program had been established we were interested in determining how the number of prematures and dystrophics had changed since the initiation of the program. For this purpose all deliveries in our hospital in 1973 were compared with those of 1974 and 1975. The newborns of the surveillance program were analysed as a separate group. For all groups infants with a birthweight of equal to or less than 2700 grams were classified as either hypotrophic mature infants, eutrophic prematures, or hypotrophic prematures. Results are summarized in Tab. III.

For comparison with World Health Organization criteria, a column with infants weighing equal to or less than 2500 grams is included. Column 4, lines 1, 2, 3 of Tab. III demonstrates that the total number of all low birth weight infants in our hospital between 1973 (8.6%) and 1975 (8.2%) remained virtually unchanged. A classification into the three subgroups (columns 5a–c, 4d, lines 1, 2, 3) shows that the number of prematures increased significantly ($p < 0.01$) between 1973 and 1974 but decreased weakly significantly ($p < 0.1$) between 1974 and 1975; there is a slight nonsignificant increase from 1973 to 1975. However, the number of dystrophic births since 1973 has continued to drop. The decrease between 1973 and 1975 (column 5d, lines 1 and 3) is weakly significant ($p < 0.1$). From column 4, lines 1, 2, 3, 4 it is seen that the total number of low birth weight infants in the surveillance group is lower than the corresponding total group (difference to 1973 and to 1975 not significant, but highly significant to 1974). From the classification into the 3 sub-groups it can be seen, that the surveillance group has significantly fewer prematures as compared to the total group in 1974 ($p < 0.01$) and 1975 ($p < 0.1$) respectively. The number of dystrophic infants between the surveillance group and the entire group in 1973, 1974, and 1975 is not significantly different. Considering the decrease in dystrophic births from 1973 to 1975 this fact expresses that because of the increased "placental risk" the dystrophic births are increased in the surveillance group. Statistics of 1868 newborns from 1975 in 3 other obstetric services in Hamburg [17] showed that about 9.7% of the infants born in Hamburg in 1975 weighed equal to or less than 2700 grams. Of these about 4.2% were eutrophic prematures and about 5.5% were hypotrophic mature and premature infants. Thus, our surveillance group and the average in Hamburg did not differ significantly in respect to premature infants ($p > 0.1$). In respect to prematures, our total group in 1975 was slightly ($p < 0.1$%) above the Hamburg average. The number of dystrophic births in our surveillance group (3.6%) is slightly ($p < 0.1$) less than the Hamburg average but in the total group (2.6%) the difference is markedly significant ($p < 0.001$).

Tab. III. Statistics of premature and dysmature births from 1973 to 1975

Column	1	2	3		4		5a		5b		5c		5d	
							birth weight ⩽ 2700 g							
Line		N	birth weight ⩽ 2500 g	%	⩽ 2700 g	%	hypotrophic mature	%	eutrophic premature	%	hypotrophic premature	%	5a + 5c	%
1	1973	1143	58	5.1	98	8.6	43	3.8	51	4.5	4	0.3	47	4.1
2	1974	1069	70	6.5	123	11.5	36	3.3	82	7.7	5	0.5	41	3.8
3	1975	920	47	5.1	76	8.2	23	2.5	52	5.6	1	0.1	24	2.6
4	surveillance group since January 1974	500	18	3.6	35	7.0	17	3.4	17	3.4	1	0.2	18	3.6

3 Discussion

From our recently described endocrine model [18] it may be expected that a pathological hormonal status between the 20th and 27th week should primarily consist of abnormal pregnanediol findings. In 105 women (88.2%) of a total of 119 with pathological hormonal status the pregnanediol excretion only was pathological. Thus, our expectations were confirmed and our model was further corroborated. **There is a highly significant correlation between the presence of "placental risk" (Tab. II) and the hormonal status (Tab. I) as well as between mean birth weight and hormonal status (Tab. I).** Thus, it has been further proven that pregnanediol excretion as determined by our method [20] represents a very sensitive early indicator of decreased nutritive placental function. This result is the more surprising since most authors [1, 8, 11 and others] do not consider pregnanediol excretion as a suitable indicator of nutritive placental function. Whether the contradictory experiences of other authors with pregnanediol are based on the variations in methodology must await further investigation. With the aid of pregnanediol excretion the diagnosis of beginning "placental insufficiency" can be made as early as between the 20th and the 27th week. In this stage of pregnancy the fetus is normally not yet impaired in his growth and consequently estrogen excretion is usually within the normal range. The hormonal status in only three cases of hypotrophic newborns (16.6% of all hypotrophic infants or 0.6% of all newborns of the surveillance group) was normal between the 20th and 27th week. Even if the pregnancies did show a "placental risk" they resulted in 39 of 41 cases in a normal mature infant if the hormonal status was normal. From this and from the very highly significant correlation between mean birth weight and hormonal status it follows that the hormonal findings between the 20th and 27th week do not only give an information about the actual functional state of the placenta but also allow a relatively accurate prognosis about the further course of pregnancy and fetal growth.

However, this includes a relatively high proportion of "false pathological" hormonal findings. It is difficult to assess how high this proportion actually is. In addition to methodological limitations and uncertainties (losses during the analytical procedure) which cannot be abolished entirely, a "false pathological" hormonal status can also be explained on morphological reasons. It is known that the placenta has considerably capabilities for compensation i.e. morphologically in particular the ability of the new formation of endocrine active syncytiotrophoblast from LANGHANS' cells [5, 6, 7]. Possibly this finds an endocrine expression in (insufficient syncytiotrophoblast) later becomes normal or tends towards normalization as has been observed by us [18]. Even a failure of pregnanediol excretion to normalize does not necessarily indicate a clinically manifest fetal growth retardation. In cases of pathological pregnanediol excretion during the entire second half of pregnancy with simultaneously normal weight infants we usually observe a normal estrogen rise until delivery. Evidently, in these cases the residual capacity of the placenta is sufficient for normal fetal supply. Thus, it is possible that our patient groups contain a higher number of these mild, possibly transient forms of placental insufficiency because in comparison to a hypothetical group of randomily selected patients more than twice the number of cases with "placental risk" are included in the survey. This indicates a certain selection of the patients by the referring obstetricians who collaborated with us even though a selection was not initially planned. A clinically unremarkable course of pregnancy or the normal weight of a newborn do not prove that the placental function has been entirely normal throughout. It is obviously important for obstetric management that the number of "false normal" findings is low. This condition is met by our program.

It would be desirable to carry out endocrine surveillance in all pregnancies between the 20th and 30th week at a time when the placental indicators are of particular significance. After the 30th week, estrogen excretion as an indicator of fetal growth assumes greater importance without any doubt.

The total number of prematures in our hospital was not significantly decreased by the endocrine surveillance, even though the surveillance group did contain significantly less prematures than the total patient population in 1974 and 1975 (Tab. III). We had determined earlier [18] that there is not

always a correlation between premature onset of labor and the excretion of hormones. It is remarkable, however, that the prematures with normal hormonal status were most typically eutrophic premature (Tab. I). Evidently, in these cases, the premature onset of labor is not brought on by a utero-placental insufficiency, but possibly more by a neuroexcitatory hypersensibility [4]. The primary indication for hormonal analysis is the diagnosis of chronic impairment of nutritive placental function. Therefore, one should expect from an endocrine surveillance program, a decrease in the number of dystrophic births. We were able to prove that (Tab. III, column 5d, lines, 1, 2, 3). Our results to the best of our knowledge also represent the only tabulation in which there is a marked decrease of hypotrophic newborns between 1973 and 1975. We consider two factors as responsible: early diagnosis by determination of pregnanediol excretion after the 20th week and resulting timely long-term preventive measures.

There is a wide-spread opinion that hormonal assays in 24 hour urines are not practicable in ambulatory practice because of the uncertainty of proper collecting techniques. We do not find this to be true. **The number of hormonal assays which could not be analysed properly because of faulty urine collections in our study (as identified by creatinine determinations) is negligibly low.** In our experience only two conditions need to be met in order to demonstrate practicability in this respect: 1. there must be no language barriers; 2. the patient must be motivated. There should be little argument that pregnant women are particularly easily motivated.

Summary

The prognostic value of hormonal assays in pregnant women during the second trimester in regard to the risk for premature and dysmature births was studied. Based on a recently published endocrine model, since early 1974 we performed three combined total estrogen and pregnanediol assays in the 24 hour urine in 500 "unselected" women between the 20th and 27th week of gestation. We believe this to be the first description of a **systematical endocrine surveillance program in this early stage of gestation.** The current study uses a fundamentally different approach than has been used thus far in perinatal medicine, where hormonal assays are carried out only after the 30th week of gestation. These then left often only the decision whether the pregnancy should be terminated prematurely. Thus, intrauterine fetal death but not intrauterine growth retardation and frequently associated irreversible brain damage of the infant might be avoided. This procedure represents a dead-end street in so far as it may aid in lowering perinatal mortality but not perinatal morbidity. The early starting point of our surveillance (20th week) was chosen because we think that premature termination of pregnancy is not necessarily the only consequence when dealing with "placental insufficiency." If this emergency solution is to be avoided, two prerequisites must be met: 1. early diagnosis of placental functional disturbance and 2. timely long-term preventive measures. **Hormonal diagnosis, in our opinion, is currently the only chance for early recognition of disturbed nutritive placental function acceptable to large scale use.** All other indicators (ultrasound, fundus height, etc.) show pathological results only after the disturbed growth of the fetus is already manifest and time for treatment has passed.

Gestational age was measured by means of ultrasonographic determination of the biparietal skull diameter in the 20th week. Hormonal assays were divided into two groups, normal and pathological. With normal hormonal assays the patient was further monitored endocrinologically only if there were concurrent clinical placental risk factors. With pathological hormonal findings the assays were repeated during a following control period of several weeks. Women with increased pathological findings (10% of the total group) were further cared for in an intensive program and will be reported on separately. Hormonal findings were statistically correlated to the birth weight of the children and a defined "placental risk" from history or current pregnancy. We then compared internally our premature and dysmature births from 1973 to 1975. For this purpose the children equal to or under 2700 grams were classified as hypotrophic mature, eutrophic premature and hypotrophic premature. This study had the following results:

1. The endocrine model described by us was again confirmed. From the pathological hormonal findings 88.2% were due to pathological pregnanediol excretion (N = 105), only 3.3% (N = 4) due to pathological estrogen excretion, the remainder (N = 10) had both pathological estrogen and pregnanediol excretion. Thus, the endocrine surveillance was 119 times pathological (23.8% of all pregnancies, **Tab. I**).
   According to our model fetuses who later become hypotrophic in this early stage of pregnancy usually are in risk group II (10 of 15). There were too few cases to allow percentage calculations of the hypotrophic newborns in correlation with the corresponding risk groups. However, as early as the 20th to 27th week, the same risk tendencies are recognizable as have been recently described for a group of 222 pregnant patients in later stages of pregnancy: the risk of intrauterine growth retardation increases markedly from risk group I (0.7% hypotrophic infants) via II (10 of 105 newborns hypotrophic) and III (one newborn of four hypotrophic) to risk group IV (four newborns of 10 hypotrophic).
2. **There is a highly significant correlation between pregnanediol excretion by our method and the mean birth**

weight of the newborns (Tab. I). This is further proof that pregnanediol excretion by our method is an early indicator of diminished nutritive placental function. By measuring pregnanediol excretion "placental insufficiency" can be diagnosed as early as between the 20th and 27th week.

3. A "placental risk" is defined from the patient's past history of placental risk factors and those during the current pregnancy (Tab. II). This "placental risk" is found significantly more often associated with a pathological hormonal assay than with normal hormonal assay (Tab. I). This association together with the positive correlation between pregnanediol excretion and mean birth weight prove that these factors of "placental risk" indeed are risk factors related to the placenta such as potentially early diminished nutritive function.
   With "placental risk" in the past history and currently normal hormonal assay, 39 of 41 (95.1%) infants were born mature and with a normal weight (there was one premature and one dystrophic newborn). In the absence of a "placental risk" but with pathological hormonal findings there were normal infants in 45 of 48 cases (93.7%) (one premature and two dystrophic births).
4. **In only 3 (16.6%) of 18 cases of hypotrophic newborns the hormonal results in the second trimester were normal.** In contrast the hormonal findings in 14 of 17 cases (82.3%) of eutrophic prematures was normal.
5. Points 2, 3, and 4 above allow the conclusion that in case of normal hormonal findings between the 20th and 27th week a placental risk and thus the risk of intrauterine growth retardation may be ruled out with a high degree of certainty. With pathological hormonal findings in the surveillance period it is necessary to repeat the tests during the following weeks (control period) and to select between the 30th and 33rd week those cases in which impairment of the fetus must be assumed. The latter require an intensive program until delivery.
6. The system described allows an early diagnosis of disturbed nutritive placental function and thus timely preventive measures. These include in addition to the treatment of clinical symptoms, general rest and decreased stress to the woman even before the 30th week, possibly longer periods of bed-rest if necessary. The incidence of hypotrophic newborns in our hospital decreased noticably from 1973 to 1975 (Tab. III). It was not possible to decrease the number of eutrophic prematures.
   The incidence of prematurity in 1975 when compared between our hospital (5.6%) and the average in our region (about 4.2%) is not significantly different. However, the difference in the number of dystrophic newborns in 1975 between our hospital (2.6%) and the average in Hamburg (about 5.5%) is significantly different ($p < 0.001$).
7. An ambulatory endocrine surveillance program utilizing 24 hour urine collections is practicable if two conditions are met: 1. there must be no language barrier with the patient, and 2. the patient must be informed and motivated.
8. We consider the results of this study a strong argument in favor of extending the protective period provided for pregnant women in the occupational health regulations of the Federal Republic of Germany.

Keywords: Endocrine surveillance program, intrauterine growth retardation, nutritive placental function, pregnanediol, total estrogens.

Zusammenfassung

Prognostischer Wert der kombinierten Gesamtöstrogen- und Pregnandiolbestimmung im 24-Stunden-Urin, demonstriert an 500 Schwangerschaften eines endokrinologischen Vorsorgeprogramms im II. Trimenon

Es wird über eine systematische Studie zur Prüfung des prognostischen Wertes von Hormonanalysen bei Schwangeren im II. Trimenon hinsichtlich des Risikos der Früh- und Mangelgeburt berichtet. Auf der Basis eines kürzlich veröffentlichten endokrinologischen Modells wurden seit Anfang 1974 bei 500 „unausgewählten" Schwangeren zwischen der 20. und 27. Schwangerschaftswoche drei kombinierte Gesamtöstrogen- und Pregnandiolbestimmungen im 24-Stunden-Urin durchgeführt. Es handelt sich unseres Wissens um die erstmalige Beschreibung eines **systematischen endokrinologischen Vorsorgeprogramms aus diesem frühen Schwangerschaftsstadium.** Die vorliegende Studie beschreitet damit einen prinzipiell anderen Weg als es bisher in der Perinatalmedizin üblich war. Bekanntermaßen werden Hormonanalysen meist erst nach der 30. Schwangerschaftswoche durchgeführt. Sie dienen dann oft nur der Entscheidung, ob die Schwangerschaft vorzeitig beendet werden muß oder nicht. Dadurch können zwar der intrauterine Fruchttod, jedoch nicht die intrauterine Wachstumsverzögerung und die damit häufig verbundenen irreversiblen zerebralen Schäden des Kindes verhindert werden. Das bisher übliche Vorgehen ist insofern eine Sackgasse, als es zwar die perinatale Mortalität, jedoch nicht die perinatale Morbidität zu senken vermag. Der Beginn unseres Programms (20. Woche) wurde deshalb so früh gewählt, weil wir der Ansicht sind, daß vorzeitige Schwangerschaftsbeendigung nicht notwendigerweise die einzige Konsequenz bei „Plazentarinsuffizienz" zu sein braucht. Will man diese Notlösung vermeiden, müssen allerdings zwei Voraussetzungen erfüllt sein: 1. Frühdiagnose der Plazentafunktionsstörung und 2. rechtzeitige, langfristige vorbeugende Maßnahmen. **Die Hormondiagnostik bietet nach unserer Meinung zur Zeit die einzige, in großem Umfang praktikable Chance der Früherkennung der gestörten nutritiven Plazentafunktion.** Alle anderen Parameter (Ultraschall, Fundusstand usw.) zeigen erst dann pathologische Ergebnisse, wenn die Wachstumsverzögerung des Feten schon manifest und es für eine konservierende Behandlung zu spät ist.

Das Gestationsalter wurde durch Messung des biparietalen Kopfdurchmessers mittels Ultraschall in der 20. Woche festgelegt. Die Hormonbefunde wurden in zwei Gruppen unterteilt: normale und pathologische. Bei normalem Hormonbefund wurde die Schwangere nur dann weiter endokrinologisch überwacht, wenn gleichzeitig klinische plazentare Risikofaktoren bestanden. Bei pathologischem Hormonbefund wurde nach einer mehrwöchigen anschließenden Kontrollperiode nochmals selektiert. Die Schwangeren mit gehäuften pathologischen Befunden (etwa 10% der Gesamtgruppe) wurden in einem Intensivprogramm weiter betreut. Hierüber wird gesondert berichtet. Die Hormonbefunde wurden in statistische Beziehung gesetzt zum Geburtsgewicht der Kinder und zu einem definierten „plazentaren Risiko" aus Anamnese oder jetziger Gravidität. Es wurde dann eine interne vergleichende Statistik von Früh- und Mangelgeburten der Jahre 1973 bis 1975 erstellt. Dabei wurden Kinder ≤ 2700 g in hypotrophe Reifgeborene, eutrophe Frühgeborene und hypotrophe Frühgeborene klassifiziert.
Die Studie erbrachte folgende Ergebnisse:

1. Das von uns kürzlich beschriebene endokrinologische Modell konnte erneut bestätigt werden. Von den pathologischen Hormonbefunden entfielen 88,2% auf pathologische Pregnandiolausscheidung (N = 105), nur 3,3% (N = 4) auf pathologische Östrogenausscheidung, der Rest (N = 10) auf pathologische Östrogen- und Pregnandiolausscheidung. Der endokrinologische Gesamtbefund war somit 119mal pathologisch (23,8% aller Schwangerschaften, **Tab. I**).
   Unserem Modell entsprechend finden sich die meisten später hypotrophen Kinder in diesem frühen Schwangerschaftsstadium noch in Risikogruppe II (10 von 15). Für eine prozentuale Aufschlüsselung der hypotrophen Neugeborenen in Abhängigkeit von der jeweiligen Risikogruppe ist die Fallzahl zu gering. Jedoch ist bereits zwischen der 20. und 27. Woche die gleiche Risikotendenz erkennbar, wie sie kürzlich für eine Gruppe von 222 Schwangeren aus späteren Schwangerschaftsstadien beschrieben wurde: das Risiko der intrauterinen Mangelentwicklung wächst erheblich von Risikogruppe I (0,7% hypotrophe Kinder) über II (10 Neugeborene von 105 hypotroph) und III (1 Neugeborenes von 4 hypotroph) nach Risikogruppe IV (4 Neugeborene von 10 hypotroph).
2. **Es besteht ein sehr hoch signifikanter Zusammenhang zwischen der Pregnandiolausscheidung nach unserer Methodik und dem mittleren Geburtsgewicht der Neugeborenen** (Tab. I). Dies ist ein weiterer Beweis, daß die Pregnandiolausscheidung nach unserer Methodik einen Frühparameter bei eingeschränkter nutritiver Plazentafunktion repräsentiert, wie bereits kürzlich berichtet wurde. Mit Hilfe der Pregnandiolausscheidung läßt sich „Plazentarinsuffizienz" schon zwischen der 20. und 27. Woche diagnostizieren.
3. Es wird ein „plazentares Risiko" definiert, das aus plazentaren Risikofaktoren der Anamnese oder der jetzigen Gravidität besteht (**Tab. II**). Bei pathologischem Hormonbefund tritt „plazentares Risiko" sehr hoch signifikant häufiger auf als bei normalem Hormonbefund (Tab. I). Unter Einbeziehung der positiven Korrelation zwischen Pregnandiolausscheidung und mittlerem Geburtsgewicht ist dadurch gleichzeitig bewiesen, daß die genannten Faktoren des „plazentaren Risikos" tatsächlich plazentare Risikofaktoren im Sinne einer potentiellen Beeinträchtigung der nutritiven Funktion sind.
   Bei „plazentarem Risiko" in der Anamnese und jetzt normalem Hormonbefund wurde in 39 (95,1%) von 41 Fällen ein reifes, normalgewichtiges Kind geboren (eine Frühgeburt, eine Mangelgeburt). Bei Fehlen eines „plazentaren Risikos" und pathologischem Hormonbefund wurde in 45 (93,7%) von 48 Fällen ein reifes, normalgewichtiges Kind geboren (eine Frühgeburt, zwei Mangelgeburten).
4. **Nur in 3 (16,6%) von insgesamt 18 Fällen hypotropher Neugeborener war der Hormonbefund im II. Trimenon normal.** Dagegen war der Hormonbefund in 14 (82,3%) von insgesamt 17 Fällen eutropher Frühgeborener normal.
5. Aus 2, 3 und 4 folgt, daß im Falle eines normalen Hormonbefundes zwischen der 20. und 27. Woche ein plazentares Risiko und damit das Risiko der intrauterinen Wachstumsverzögerung relativ sicher ausgeschlossen werden können. Bei pathologischem Hormonbefund in der Vorsorgeperiode ist es erforderlich, nach einer weiteren mehrwöchigen Kontrollperiode in der 30.–33. Woche diejenigen Risikofälle zu selektieren, bei denen eine Bedrohung des Feten angenommen werden muß. Letztere erfordern eine Intensivbetreuung bis zur Entbindung.
6. Das beschriebene System gestattet eine Frühdiagnose von Störungen der nutritiven Plazentafunktion und somit rechtzeitige, vorbeugende Maßnahmen. Darunter verstehen wir neben der Behandlung einer eventuellen klinischen Symptomatik vor allem eine allgemeine Entlastung der Patientin schon vor der 30. Woche, falls erforderlich mit längeren Liegeperioden. Die Zahl der hypotrophen Neugeborenen konnte dadurch an unserer Klinik von 1973 bis 1975 deutlich gesenkt werden (**Tab. III**). Die Zahl der eutrophen Frühgeborenen konnte nicht gesenkt werden.
   In der Frühgeburtenhäufigkeit des Jahres 1975 besteht zwischen unserer Klinik (5,6%) und dem lokalen Durchschnitt (ungefähr 4,2%) kein wesentlicher Unterschied. Jedoch ist der Unterschied in der Mangelgeburtenhäufigkeit des Jahres 1975 zwischen unserer Klinik (2,6%) und dem Hamburger Durchschnitt (ungefähr 5,5%) sehr hoch signifikant ($P < 0{,}001$).
7. Ein ambulantes endokrinologisches Vorsorgeprogramm auf der Basis von 24-Stunden-Urin ist unter zwei Voraussetzungen praktikabel: 1. Es muß eine sprachliche Verständigung mit der Patientin möglich sein. 2. die Patientin muß informiert und motiviert werden.
8. Wir meinen, daß das Ergebnis der vorliegenden Studie ein starkes Argument zur Verlängerung der Mutterschutzfrist in der Bundesrepublik darstellt.

Schlüsselwörter: Endokrinologisches Vorsorgeprogramm, Gesamtöstrogene, intrauterine Wachstumsverzögerung, nutritive Plazentafunktion, Pregnandiol.

Résumé

Valeur pronostique de la définition combinée d'oestrogène total et de prégnandiol des urines de 24 h., démontrée à l'aide de 500 grossesses dans le cadre d'un programme prophylactique endocrinologique au IIème trimestre

L'article présent porte sur l'étude systématique de la valeur pronostique des analyses hormonales au cours du IIème trimestre de la grossesse en ce qui concerne le risque d'accouchement prématuré ou carenciel. Nous référant à un exemple endocrinologique publié récemment, nous avons effectué trois définitions combinées d'oestrogène total et de prégnandiol des urines de 24 h entre la 20ème et la 27ème semaine de grossesse chez 500 femmes enceintes «prises au hasard» depuis le début de 1974. A notre connaissance c'est la première fois qu'a été établi **un programme prophylactique endocrinologique systématique pour ce stade précoce de la grossesse.** L'étude présente trace donc une voie dont le principe diffère de ce qui était courant jusque là en médecine périnatale. Comme on sait, les analyses hormonales ne sont effectuées en général qu'après la 30ème semaine de grossesse et ne servent donc souvent qu'à décider s'il est nécessaire de terminer prématurément la grossesse. Ceci permet, certes, d'empêcher la môt embryonnaire intra-utérine, mais non le retard de croissance intrautérine qui entraîne souvent des lésions cérébrales irréversibles chez l'enfant. Le procédé employé jusque là s'avère donc insuffisant dans la mesure où il permet de faire baisser seulement le taux de mortalité, mais non de morbidité périnatale. Le début de notre programme (20ème semaine) a été fixé si tôt parce que nous estimons que la fin prématurée de la grossesse n'est pas nécessairement la seule mesure conséquente à prendre en cas d'«insuffisance placentaire». Toutefois, pour éviter cette solution d'urgence, il faut remplir au préalable les deux conditions suivantes: 1. Diagnostic prématuré du trouble fonctionnel placentaire et 2. mesures prophylactiques à long terme appliquées à temps. **Le diagnostic hormonal offre actuellement à notre avis la seule chance largement praticable du dépistage précoce de la fonction placentaire nutritive perturbée.** Tous les autres paramètres (ultra-son etc...) ne donnent des résultats pathologiques que lorsque le retard de croissance du foetus apparaît déjà avec évidence et qu'il est trop tard pour appliquer un traitement conservatif.

L'âge de gestation a été fixé grâce à l'examen ultrasonique (mesure du diamètre crânien biparíétal) dans la 20ème semaine de grossesse. Les résultats hormonaux ont été divisés en deux groupes: normaux et pathologiques. Dans les premiers cas on n'a continué un contrôle endocrinologique que lorsque subsistaient des facteurs de risque placentaires cliniques. Dans les seconds cas il a été procédé à une nouvelle sélection après plusieurs semaines consécutives de surveillance. En cas de résultats pathologiques répétés (10% environ de tout le groupe) les femmes enceintes ont été soignées dans le cadre d'un programme intensif qui est décrit à part. Un rapport statistique a été établi entre, d'une part, les résultats hormonaux et, d'autre part, le poids des enfants à la naissance ainsi qu'un «risque placentaire» défini à partir de l'anamnèse ou de la gravidité présente. Puis nous avons effectué une statistique comparative interne des accouchements prématurés et carenciels pour les années 1973 à 1975. Les enfants ⩽ 2700 g ont été classés en nouveaux-nés «matures» hypotrophes, prématurés eutrophes et prématurés hypotrophes.

L'étude a fourni les résultats suivants:

1. L'exemple endocrinologique que nous avons explicité récemment a pu être de nouveau confirmé. Parmi les résultats hormonaux pathologiques, 88,2% relevèrent d'une élimination pathologique de prégnandiol (N = 105), 3,3% seulement (N = 4) d'une élimination pathologique d'oestrogène et le reste (N = 10) d'une élimination pathologique d'oestrogène et de prégnandiol, c.à.d. que l'ensemble des résultats endocrinologiques a été 119 fois pathologique (23,8% de toutes les grossesses, **Tab. I**).
   Correspondant à notre modèle, la majorité des enfants plus tard hypotrophes se trouvent encore dans le groupe de risque II (10 sur 15) en ce stade précoce de grossesse. Le nombre des nouveaux-nés hypotrophes concernés dans notre étude est trop réduit pour permettre d'établir un pourcentage pour chaque groupe de risque respectif. Toutefois, la même tendance de risque est déjà décelable entre la 20ème et la 27ème semaine de grossesse ainsi qu'elle a déjà été décrite récemment pour un groupe de 222 femmes enceintes en stade tardif de grossesse: le risque de malnutrition intrautérine augmente considérablement du groupe de risque I (0,7% des enfants sont hypotrophes) aux groupes de risque II (10 enfants hypotrophes sur 105 nouveaux-nés) et III (1 enfant hypotrophe sur 4 nouveaux-nés) jusqu'au groupe de risque IV (4 enfants hypotrophes sur 10 nouveaux-nés).
2. **Il existe un rapport très significatif entre l'élimination de prégnandiol d'après notre méthode et le poids moyen de naissance des nouveaux-nés** (Tab. I). Ceci est une preuve de plus qu'en accord avec notre méthode l'élimination de prégnandiol représente un paramètre précoce pour une fonction placentaire nutritive réduite ainsi que nous l'avions relaté récemment. L'analyse de l'élimination de prégnandiol permet de diagnostiquer une «insuffisance placentaire» dès la période située entre la 20ème et la 27ème semaine de grossesse.
3. Nous avons défini un «risque placentaire» qui résulte de facteurs de risque placentaires de l'anamnèse ou de la gravidité présente (**Tab. II**). En cas de résultats hormonaux pathologiques, le «risque placentaire» apparaît beaucoup plus fréquemment d'une façon statistiquement très significative que dans les cas de résultats normaux (Tab. I). Si on inclut la corrélation positive entre l'élimination de prégnandiol et le poids moyen à la naissance, on prouve en même temps que les facteurs précités de «risque placentaire» sont effectivement des facteurs de risque placentaires dans le sens d'une restriction potentielle de la fonction nutritive.
   Dans les 39 des 41 (95,1%) cas de «risque placentaire» de l'anamnèse et de résultats hormonaux présentement normaux, les nouveaux-nés ont eu un poids normal et étaient «matures» (les deux autres cas ont été un accouchement prématuré et un accouchement carenciel).
   Dans 45 des 48 (93,7%) cas sans «risque placentaire» mais avec résultats hormonaux pathologiques, les nouveaux-nés ont eu un poids normal et étaient

«matures» (les 3 autres cas ont consisté en un accouchement prématuré et 2 accouchements carenciels).

4. **Dans seulement 3 des 18 (16,6%) cas de nouveaux-nés hypotrophes, les résultats hormonaux du IIème trimestre étaient normaux.** Par contre, dans 14 des 17 (82,3%) cas de prématurés eutrophes, les résultats hormonaux étaient normaux.
5. Des résultats 2, 3 et 4 il ressort qu'en cas de résultats hormonaux normaux entre la 20ème et la 27ème semaine, un risque placentaire et, par là, le risque du retardement de croissance intra-utérine peuvent être exclus avec une certitude relativement absolue. Dans les cas de résultats hormonaux pathologiques dans la période préventive, il est nécessaire de sélectionner après plusieurs semaines de contrôle, c.à.d. entre la 30ème et la 33ème semaine de grossesse, les cas de risque qui font présager un risque pour le foetus. Ces derniers exigent une surveillance intensive jusqu'à l'accouchement.
6. Le système décrit permet d'établir un diagnostic précoce de troubles de la fonction placentaire nutritive et de prendre ainsi à temps des mesures prophylactiques qui comprennent surtout, outre le traitement de symptômes cliniques éventuels, un soulagement général de la patiente dès avant la 30ème semaine avec, si nécessaire, de longues périodes de repos allongé. Cela a permis d'abaisser sensiblement le nombre des nouveaux-nés hypotrophes à notre clinique entre 1973 et 1975 (Tab. III), mais non celui des prématurés eutrophes. Il n'existe pas de différence substantielle dans la fréquence des accouchements prématurés de 1975 entre notre clinique (5,6%) et la moyenne locale (4,2% environ). Par contre, la différence de fréquence des accouchements carenciels en 1975 a été très forte ($P < 0{,}001$) entre notre clinique (2,6%) et la moyenne de Hambourg (5,5% environ).
7. Un programme prophylactique endocrinologique en consultation externe basé sur l'analyse des urines de 24 h. est praticable aux deux conditions suivantes: 1. Il faut pouvoir être sûr de bien se faire comprendre par la parturiente. 2. Celle-ci doit être informée et «motivée».
8. Nous estimons que les résultats de l'étude présente constituent un argument solide en faveur d'une prolongation du délai de protection maternelle en RFA.

Mots-clés: Fonction placentaire nutritive, oestrogènes complets, prégnandiol, programme prophylactique endocrinologique, retardement de la croissance intra-utérine.

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Dr. rer. nat. Reinhold Wolfrum
Allgemeines Krankenhaus Heidberg
Chemische Abteilung
Tangstedter Landstraße 400
D-2000 Hamburg 62